The Current Impact of Human Papillomavirus Vaccines on Population Health

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Both locally and globally, Human Papillomavirus (HPV) affects millions of people every year not discriminating based on gender, socioeconomic status, age, or health history. Persistent HPV infection has been linked to cancers of the mouth/throat, penis, anus, rectum, and most famously cervical cancer. The utilization and application of Human Papillomavirus (HPV) vaccines are drastically reducing the prevalence of HPV in vaccine recipients. A severe lack of HPV and HPV vaccine education are limiting the protective ability of these vaccines. Becoming available only as recently as 2006 there is a lack of HPV education, longitudinal research on long-term efficacy, and moral dilemmas among parents that negatively effect vaccine uptake. The purpose of this manuscript is to educate about HPV, HPV mechanisms of action, demographic information, and the consequences of HPV infection by presenting credible evidence. Next, there will be an examination of the current research on HPV vaccinations, the controversies surrounding them, and the current recommendations for HPV protection. Seeing reductions in HPV and its consequences will help guide Oklahoma, the US, and the world to enact HPV vaccination policies that decrease HPV infection prevalence and thereby increase the health of the population.

HPV Infection and Cervical Cancer

First, a detailed knowledge of Human Papillomavirus is crucial to understanding HPV vaccination. HPV is the most common sexually transmitted infection and there are over 100 HPV genotypes, which are identified numerically by their discovery [1]. HPV infection is transmitted from person to person during vaginal, anal, or oral sex. Typically, symptoms do not develop with HPV infection making it easy to spread because individuals may not know they are infected. If symptoms do arise they typically manifest themselves as genital warts. Most HPV infections are cleared within 2 years, some are sooner and some are longer. Frequent Pap smears

are a good way to monitor current infection and watch for signs of persistent infection or tissue abnormalities [2]. Those with autoimmune disorders, such as human immunodeficiency virus (HIV) that lower the body's ability to fight disease, injuries, or who are currently fighting disease may be unable to overcome the infection alone. However, the immunosuppressed are not the only population who may be unable to clear HPV infection. Similar to the contracting the flu or another infection, people who are tired, stressed, as well as those who are not getting adequate nutrition are also all at a higher risk of not clearing the infection.

Even when HPV is cleared a person who is sexually active is at risk for contracting HPV again. Additionally, HPV may be dormant for years or recede into periods of latency and return more problematic and deft to the immune system. Both reinfection and latent infection can cause persistent HPV infection, which has been shown to be the cause of 98% of cervical cancer cases, the fourth most frequent cancer in women [3]. Knowing that 98% of cervical cancer cases and deaths are attributed to HPV, it is possible to greatly decrease the current 530,000 annual new cases of cervical cancer worldwide, of which 270,000 deaths were estimated in 2012 alone [3]. Based on this information there is potential for an effective vaccine to drastically decrease infection prevalence and transmission.

HPV is a double stranded DNA virus from the Papillomaviridae family of DNA viruses, which are distinguished from other families of viruses because of their control over gene expression allowing the virus to take control of the cell's synthetic machinery[4]. Additionally, DNA viruses in this family take control of a cell's nucleus and have the ability to remain latent or dormant for extended amounts of time. HPV virus is packaged in a protein capsid that totals 8000 base pairs in length [1]. Mechanistically, the virus infects by attaching to the basal keratinocytes of the cervical epithelium in females or the penile or anal epithelium in men

through existing micro-abrasions in the layer. At this point a healthy immune system would typically recognize pro-inflammatory cytokines such as IL-12, IL-18, IFN-γ, and IL-6 produced by macrophages that were activated by the invaded epithelial cells [4].

However, in persistent infection the viral genome becomes merged to the host genome, a process called homologous recombination, which causes an overexpression of viral E6 and E7 genes [5]. Homologous recombination is a process that releases nucleases, which induce double-stranded DNA breaks, and then repairs the break with the invading virus DNA[6]. The cell begins to replicate viral DNA as if it were the original cell's DNA utilizing the cells already present machinery. HPV replication begins with initiating transcription of the viral E6 genes that damage and deregulate p53 genes, tumor-suppressor genes, which function to maintain a proper cell cycle including growth, division, and death of cells[7]. Without this regulation, mutated cells do not undergo apoptosis and mutated DNA begins to collect, eventually causing dysplasia of the cervical epithelium [8]. The other protein that is overexpressed in persistent HPV infection is E7, which degrades Retinoblastoma protein; a protein responsible for regulating the S-phase of cell replication. Disruption of the checkpoints before the S-phase result in increased and unregulated cell replication [8].

HPV Vaccines on The Market

This unrestricted cell proliferation leads to tissue dysplasia and neoplasia, which is the abnormal cytology indicating cancer. The HPV genotypes are numbered in order of discovery, but are categorized by oncogenic potential. Genotypes 16 and 18 are the most cancer causing of all the known HPV genotypes. HPV 16 is responsible for approximately 50% of all cervical cancer cases and HPV 18 is attributed 15-20% of all cases [1]. The first HPV vaccine, bivalent Cervarix (2vHPV), was designed to protect from these two HPV genotypes specifically. Since its

introduction however, several more HPV genotypes have been classified as high-risk or oncogenic. HPV 16, 18, 31, 33, 34, 39, 45, 51, 52, 56, 58, 59, and 66 are the currently known high-risk HPV genotypes. The more recent quadrivalent vaccine, Gardasil (4vHPV) provides protection from genotypes 16, 18, 6, and 11. Most recently, Gardasil 9 (9vHPV) protects from these four genotypes and 31, 33, 45, 52, and 58 additionally [9]. These vaccines are aimed at avoiding the predecessor of cervical cancer, cervical intraepithelial neoplasia (CIN), which is graded from 1 to 3 (most severe). CIN1 lesions are typically cleared by a healthy immune system, but if they proceed to CIN2/3 it is estimated that 30 to 50% will ultimately progress to invasive cervical cancer[8]. However, with the use of a HPV vaccine, the aforementioned CIN1 lesions rarely develop into mature cervical cancer because the antibodies produced in response to the vaccine prevent the virus from binding to the epithelium and causing infection [4].

HPV Vaccines

Knowing what HPV is and how it operates, HPV vaccines are aimed at creating B-memory cells before a person's exposure to HPV to prevent persistent infection. All three of the current HPV vaccines on the market are of the same type and utilize the same mechanisms to generate an immune response. HPV vaccines are protein subunit vaccines, which present an antigen, a protein used to induce an immune response, to the immune system to promote the activation of the immune system and the formation of memory cells [10]. Subunit vaccines do not contain any live vaccine therefore they are extremely safe and there is absolutely no risk of contracting the disease from the vaccine. However, because there is no live portion of the virus in the vaccine, vaccine manufactures must take extra care to analyze and select the subunits of the pathogen that contain the antigenic properties to present to the immune system. There is also less certainty that the vaccine will create enough memory and plasma cells from B-cells with the

ability to produce antibodies to ward off future infection. For this reason the vaccine is given in either two or three doses several months apart [10].

The virus-like proteins (VLP) that mimic HPV genotypes are grown in yeast cells by combining genetic material from the virus. Next, the VLPs are removed from yeast cells and purified, combined with a catalyst and purification buffer [11]. The catalyst that the VLPs are combined with is called an adjuvant; a substance that enhances and controls the magnitude of the immune response [7]. There are only a handful of adjuvants and alum, an aluminum salt-based adjuvant (aluminum hydroxyphosphate sulfate), is the substance added to HPV vaccines to increase the immune response [11]. Alum signals myeloid differentiation primary response gene 88 (MyD88) and TIR-domain-containing adapter-inducing interferon-beta (TRIF). Both MyD88 and TRIF activate Toll-like receptors (TLRs), beginning the signal cascade that produces proinflammatory cytokines and chemokines as well as recruiting immune cells [12]. A more detailed explanation of the mechanisms that produce these cytokines and immunity follows.

Vaccine Mechanism

Picture yourself as a small molecule of HPV virus-like protein that is about to be intramuscularly injected into a HPV vaccine recipient. Epithelial cells, T-cells, B-cells, and many other cells in response to the vaccine entering the body produce Proinflammatory cytokines such as IL-12, IL-18, and IFN-γ. As the vaccine enters the body, immature dendritic cells surrounding the injection site take it up. Inside these cells, the protein-adjuvant combination is processed through the endosomal pathway and is broken down in the phagolysosome and bound to major histocompatibility complex type II (MHC II) molecules forming a MHC II: protein-adjuvant complex [13].

The MHC II: protein-adjuvant complex returns to the dendritic cell surface as the activated cell proceeds along the lymph channel and runs into immature T helper 2 cells (TH2). This TH2 cell is activated when the MHC II complex binds with the TH2 receptor; the TH2 cell begins rapid proliferation[13]. As all of this was happening, MHC II: protein-adjuvant complexes were encountering B-cells in the lymph node and binding. Now the TH2 cells and B-cells meet, this meeting is referred to as linked recognition. The B-cells are activated and become either memory cells or plasma cells, which are able to produce antibodies capable of remembering the antigen the next time it enters the body [13]. The plasma cells will continue secreting antibodies for up to two weeks after vaccination and B-memory cells will be stored in lymphoid tissues including the spleen, lymph nodes, and Peyer's patches [13].

The next time the virus enters the body the B-memory cells will begin rapidly replicating and producing plasma cells to secrete specific antibodies targeting the virus. This mechanism, called T-dependent, is how protein subunit vaccines confer immunity from a virus without giving a live and possibly contractible virus within a vaccine. These vaccines use only specific antigens from the virus to produce a memorable immune response and memory cells. The use of multiple doses, 2 or 3 in the case of HPV vaccination, is intended to present the antigens to the system adequately enough to confer lifetime HPV prevention.

The visual below is a simplified version of this type of vaccine mechanism.

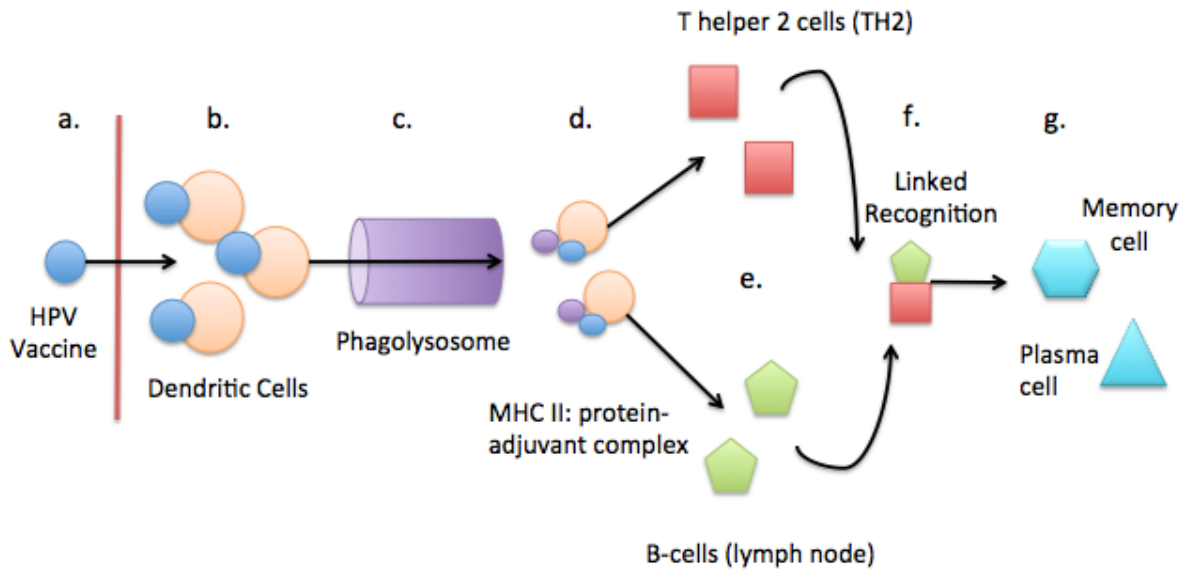

Figure 1 a. HPV vaccine (with vaccine-like proteins) is intramuscularly injected. **b.** Immature dendritic cells around the injection site take up the vaccine. **c**. The protein-adjuvant combination is broken down in the phagolysosome of the endosomal pathway and is bound to the Major Histocompatibility Complex (MHC II) forming a MHCII: protein-adjuvant complex (**d.**) **e.** MHCII: protein-adjuvant complex binds to TH2 cells in the lymph channel and B-cells in the lymph nodes, activating the TH2 cells**. f.** TH2 cells and B-cells bind, referred to as linked recognition. B-cells are activated. **g.** Activated B-cells begin rapidly producing memory cells or plasma cells. After the creation of memory B-cells and plasma cells the memory cells are stored in lymphoid tissues and are poised to begin rapid plasma cells production if the virus reenters the body. Plasma cells will produce specific antibodies able to combat the virus [13].

HPV Vaccine Efficacy

Efficacy of a new vaccine is crucial for the vaccine to initially make it out of the lab, into production, and finally implemented into mandatory vaccination lists. All three of the HPV vaccines, 2vHPV, 4vHPV, and 9vHPV, are effective at reducing the incidence of persistent HPV infection, genital warts, anal, rectal, mouth/throat, penile, and cervical cancer in men and women. Within 6 years of the Gardasil (4vHPV) vaccine introduction (2006) there was an 89% reduction in the prevalence of HPV 6/11/16/18 infection in females' ages 14-24 in comparison to unvaccinated females [9]. At the same time there was also a reduction of infection prevalence in unvaccinated females in the vaccine era compared to the prevaccine era of 17-49%. This provides evidence to support the idea that herd immunity, a high enough percentage of the population being vaccinated, protects unvaccinated members by default [9].

The first country to provide free quadrivalent HPV vaccinations (Gardasil) and try to fully implement HPV vaccination was Australia in 2007. Therefore, much of the efficacy data that researchers and consumers rely on comes out of Australia and other high vaccine utilization countries such as Finland and Sweden. Data showed that 3 years after vaccine introduction, the number of high grade cervical abnormalities (CIN1, 2, 3) was half of what it was pre-vaccine [8]. 5 years after introduction, low-grade cervical abnormalities were reduced by 34% and high-grade abnormalities by 47% in females age 12-26 in comparison to unvaccinated females from a cohort study done at introduction of the vaccine[9].

NHANES data collected during the vaccine era (2009-2012) compared to the pre-vaccine era (pre-2009) showed that HPV infections of types 6/11/16/18 decreased 64% in females aged 14-19 years and 34% in females aged 20-24 years [14]. This shows how effective HPV vaccination is in preventing persistent HPV infection and thereby preventing cervical cancer. It also provides further evidence that receiving the vaccine earlier (ages 9-13) provides more protection than receiving it later (ages 14-26). However, the vaccine has shown considerable protection as long as it is received prior to a person becoming sexually active or being infected [14].

The 9vHPV Vaccine

The most recent HPV vaccine, 9vHPV, was approved by the Food and Drug Administration in December 2014 and promises to offer greater protection by covering 9 HPV strains as opposed to Gardasil's 4 strains [15]. Clinical studies compared 9vHPV efficacy against 4vHPV by recruiting girls' ages 9-15, women ages 16-26, and men ages 16-26 who were negative for HPV at baseline and were seeking HPV vaccination. 7 months after vaccination, immunological responses are assessed by comparing geometric mean titers (GMT) of antibodies

produced based on which vaccination they received [15]. As previously thought, those vaccinated with the 9vHPV vaccine produced antibodies for HPV types 31,33,45,52, and 58 which are not protected by the 4vHPV vaccine. The immune response for the four shared HPV types, 6,11,16, and 18 were virtually identical so there is no loss of coverage with the addition of more strains [15].

Researchers have also stated that a two-dose schedule (6-12 months apart) of 9vHPV produced higher GMT levels than the traditional three-dose schedule (0, 2, and 6 months between) and therefore is recommended for boys and girls ages 9-14 [15]. Currently, the most common HPV vaccination is the 4vHPV Gardasil, but because the 9vHPV vaccine provides protection over 5 additional HPV strains the 9vHPV may replace the 4vHPV in utilization in the near future. HPV types 6/11/16/18 (those included in 4vHPV) account for nearly 70% of all cervical cancer cases, but the extra five strains of HPV covered in the 9vHPV vaccine would account for an additional 14.7% of cervical cancer cases. Increasing the vaccines ability to prevent up to 84.7% of all persistent HPV-caused cervical cancer cases. 9vHPV would also raise overall coverage of vaginal cancer 18.3%, penile cancer 8.2%, and oropharyngeal cancer 5.7%[15]. Below is a chart showing the efficacy and risk reduction of 9vHPV compared to 4vHPV [15].

Table 3 Efficacy of 9vHPV on persistent HPV infection and on cervical, vulvar, and vaginal disease (HPV types 31, 33, 45, 52, or 58) in the per-protocol efficacy population[14]

Outcome	9vHPV (N=7,099)		qHPV (N=7,105)		Risk reduction
	Cases	Cases/1,000 person-years	Cases	Cases/1,000 person-years	95% CI
Persistent infection					
≥6 months	35	2.1	810	52.4	96.0 (94.4–97.2)
≥12 months	21	1.3	544	34.5	96.3 (94.4–97.7)
Cervical, vulvar, and vaginal					
CIN1, condyloma, VIN1, and VaIN1	2	0.1	82	4.3	97.6 (91.7–99.6)
CIN2/3, VIN2/3, VaIN2/3, or worse	1	0.1	30	1.6	96.7 (80.9–99.8)
Cervical disease					
CIN1	1	0.1	69	4.0	98.6 (92.4–99.9)
CIN2/3 or worse	1	0.1	27	1.5	96.3 (79.5–99.8)
Vulvar and vaginal disease					
Condyloma	0	0.0	3	0.2	100 (–71.6 to 100)
VIN1 or VaIN1	1	0.1	12	0.6	91.7 (51.3–99.6)
VIN2/3, VaIN2/3, or worse	0	0.0	3	0.2	100 (–71.5 to 100)

Note: Adapted with permission from Joura E, Giuliano AR, Iversen O-E, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med.* 2015;372(8):711–723.[14]
Abbreviation: CI, confidence interval.

Figure 2 Efficacy of 9vHPV Vaccine [4]

The recommended dosage of two of the HPV vaccines, 2vHPV and 4vHPV is 3 times with predetermined breaks in between and twice with predetermined breaks for 9vHPV. The American College of Obstetricians and Gynecologists (ACOG) recommends 1 – 2 months between the first and second dose then 6 months between the second and third doses. However, recommendations also stipulate that completion of the vaccine series is more important than having the exact time recommendations [16]. To date, long-term trials have not shown a significant difference as long as the doses were completed.

Recommendations

The recommended age of administration is crucial in HPV vaccination. The vaccine is designed to prevent HPV infection, not to treat HPV. For this reason, it is highly recommended that males and females be vaccinated before the onset of sexual activity. For this reason, recommendations are meant to be before onset of sexual activity. ACOG and the CDC recommend vaccination for males and females at age 11-12 [12, 13]. There are catch up vaccinations available for male sup to age 21 and females up to age 26 [13]. World Health Organization recommends a two-dose schedule with 6 months in between of one of the three types of vaccines to females younger than 15 years of age. For females 15-26 they recommend the typical 3-dose schedule. A three-dose schedule is also recommended for all persons who may be immunocompromised or HIV positive [17]. Immunocompromised individuals, including those with HIV, are at an increased likelihood of having persistent HPV infection because of their reduced immune system capability and possible inability to receive vaccinations.

Cervarix (2vHPV) and Gardasil (4vHPV), the first HPV vaccine, were recommended by the CDC for the vaccination of females ages 11-12 beginning in 2006. With the HPV vaccination’s ability to decrease cervical cancer risk it was only marketed to females until 2009

when the CDC began recommending the vaccination to males in addition to females ages 11-12 [18]. The first barrier for parents deciding whether to vaccinate their sons is lack of knowledge of HPV and the HPV vaccine. Primarily, parents perceived HPV as a female disease because of its strong link to cervical cancer. However, persistent HPV infection can cause cancers of the anus, rectum, mouth/throat, and penis. Adapted Pap tests that check anal, rectal, penile, and mouth/throat cytology can identify cancerous cells [19]. However, these tests are not routine and are not currently included in the standard of care.

This is relevant to men because 11,000 men in the United States develop these cancers annually as a result of HPV [20]. Many parents overlooked the fact that even if the HPV vaccine only prevented cervical cancer, vaccinating men would reduce the number of persistent HPV cases in women dramatically because men can be carriers of the disease without ever having problems. Vaccinating the entire at-risk population provides widespread coverage for all, including those immunocompromised or unable to get the vaccination for medical reasons. This widespread coverage will lower infection prevalence as well as transmission thereby decreasing the number of HPV-associated cancer cases.

Concerns preventing high uptake of HPV Vaccine

There are multiple concerns of parents that prevent them from vaccinating their children against HPV. To begin, many adults claim HPV is a “teen disease” and will not be contracted after adolescence. However, HPV can be contracted from sexual activity with an infected individual at any age. Therefore, over 50% of the population will contract HPV at some point in their lifetime [13]. Appropriate HPV vaccination prevents persistent HPV infection up to 99% across the lifetime [21]. In a Swedish school-based study, researchers gaged parent’s opinions on HPV vaccination in boys as well as girls. Many parents voiced that having boys go unvaccinated

places all the sexual and reproductive health responsibility on females, much like many traditional ideas surrounding birth control [22]. During the interviews parents expressed that equal vaccination of boys and girls would help eliminate this traditional view of sexual and reproductive responsibility. Other pro-male vaccination parents shared that they were more hesitant vaccinating their daughters without vaccinating their sons. They had fears that perhaps the vaccination was not safe for everyone and this made them hesitant to vaccinate in the first place. If vaccination was universally recommended they would be more apt to vaccinate both children at the same time [22].

Based on the confusion and concerns surrounding male HPV vaccination the CDC has provided many resources to better educate parents on vaccinations for males and females and research has been done to quantify the immune responses in men after receiving the HPV vaccine [20]. Men show an immune response of nearly 100% sero-conversion to VLP vaccines, which is a huge increase from their traditional antibody response of 20-30% from natural HPV infection [21]. The potential to protect men from multiple cancers and at the same time protect women from persistent HPV that can lead to cervical cancer is substantial and men should continue to follow the recommended HPV vaccination schedule.

In addition to the benefit that HPV vaccines are preventative and should be administered at a young age before sexual activity, it has also been shown that earlier administration, ages 11-13, of the vaccine resulted in higher antibody titers [16]. Multiple studies have shown that age of vaccine administration has an effect on antibody production. As age of vaccination increases past the recommended 11 – 12 years old the amount of antibodies created, measured as the geometric mean titer (GMT), decreases significantly and has been shown to not be effective after approximately 26 years of age [23]. A study conducted in 2013 comparing 2 and 3-dose GMTs

of females aged 9 – 13 years with 3-dose GMTs of females aged 16 – 26 at months 7, 18, 24,and 36 showed that the 16 – 26 year old group only ever gained about half or less of the antibodies that the 9 – 13 year old [23]. Other researchers have noted that the older the age of vaccination, the lower the numbers of HPV-18 B memory cells are generated [24].

Barriers to Access

With these recommendations in mind there are still significant barriers for people to receive the HPV vaccination. A major barrier is that currently the HPV vaccine is, at current prices, a $450 out-of-pocket expense for the series [25]. This cost is a major obstacle for many parents looking to vaccinate their children as well as young adults who are interested in the catch-up vaccine. Insurance providers vary on their coverage of the HPV vaccination. Some completely cover the vaccine cost while others do not consider it a required vaccination and will cover a portion, or in some cases, none at all.

Fortunately, because of HPV vaccines' immediate impact, safety, and efficacy, it has been included as a vaccine being covered under the federally-funded program called Vaccines for Children (VFC) [26]. This program provides free vaccination from 16 diseases to protect infants, young children, and adolescents up to age 19. Children are eligible for VFC if they are Medicaid-eligible, uninsured, underinsured, American Indian, or Alaska native. These vaccines are bought at discount by the CDC and distributed to state health departments, public health agencies, and other VFC providers where people can go in and receive the vaccination[26].

Table 1 Vaccine-Preventable Diseases Covered under Vaccines For Children (VFC)					
Hepatitis A (HepA)	Hepatitis B (HepB)	Diphtheria (DTaP)	Tetanus (DTaP)	Pertussis (DTaP)	Polio (IPV)
Rotavirus (RV)	Influenza (Flu)	Chickenpox (Varicella)	Pneumococcal (PCV)	Haemophilus influenza type b (Hib)	Meningococcal (MenACWY, MenB)
Measles (MMR)	Mumps (MMR)	Rubella (MMR)	**Human papillomavirus (HPV)**		

[26]

Despite the high cost, the HPV vaccine is most certainly a cost-effective life-saving measure when compared to the cost of cervical cancer treatments. Importantly, the HPV vaccine is the only cancer vaccine in current use [27] and, like a lot of other preventable care, needs to be made more accessible and affordable. To those in the legislature who are opposed to more vaccine accessibility it should be discussed that high vaccine uptake protects the entire community through herd immunity and begins to eradicate diseases. Obstacles surrounding vaccination prevent more people from being vaccinated each year. Low vaccine uptake has raised questions of whether school requirement of HPV vaccination would increase vaccine utilization. Vaccinations rates are highest for vaccines required to enter the public school system – MMR (Measles, Mumps and Rubella), Varicella (chicken pox), Polio, TDaP (Tetanus, Diphtheria, and Pertussis), and Hepatitis B [26]. If HPV were required for entrance into the public school system many fewer parents would question having their children immunized.

Herd Immunity

Vaccines like MMR, Varicella, TDaP, and Polio as well as the HPV vaccines protect the recipient of the vaccine, but they also protect everyone else. High rates of immunity create “herd immunity”; a type of immunity afforded even to those who are unable to be vaccinated because of medical reasons [27]. The level of immunity is so high that the disease cannot survive and the population benefits by eradicating diseases such as polio, which at one time affected 16,000

people a year and none presently [28]. However, when vaccination rates drop below the required percentage of the population, say 96% for measles, there begin to be outbreaks of these diseases. In December of 2014, there was a measles outbreak in Disney Land that produced 147 positive cases for measles spanning across 15 states that could all be traced back to Disney Land during a certain time. Researchers estimated that the vaccination rate at that time was somewhere between 50-86%, well below the recommended 96% [28]. Not vaccinating children puts all children at risk to contract very preventable diseases. In 2010 the CDC estimated that nearly 40% of parents have delayed or skipped a child's vaccination [16]. By enforcing HPV vaccination for school the number of vaccine recipients would increase dramatically and immunocompromised individuals would benefit from the herd immunity as well.

Political Policy on Vaccinations

The responsibility to create and enforce vaccine policy is dependent on state government, not federal. Each state is responsible for passing laws to enforce vaccinations for school children. State legislatures are also responsible for deciding what types of exemptions they will accept including and or limited to: medical, philosophical, religious, and personal exemptions. All states currently allow medical exemptions, but following the Disney Land measles outbreak the state of California signed a bill into law that abolished the personal exemptions for child vaccinations and saw increases in vaccine compliance [16]. In Oklahoma, under Oklahoma Statute 70, section 1210.192 medical, religious, and personal exemptions are allowed. There are fees associated with these vaccinations, but they are still available to anyone who wants to opt out. Additionally, Oklahoma does not require vaccine education during the exemption process [29].

In 2015, Senator Ervin Yen from Oklahoma City filed Senate Bill 830 (SB 830) that would remove personal and religious exemptions from the current state laws. As of February

2016, SB 830 did not make it out of committee and therefore will not be made into law. [29]. This bill and others like it would not immediately require the HPV vaccine for all school children, but would prevent personal exemptions from the existing required vaccines and would move Oklahoma closer to the 42 states and territories that have introduced legislation concerning the administration and requiring of the HPV vaccination. Of these, Virginia, Washington D.C., and Rhode Island are currently the only territories where the HPV vaccine is required for school [30]. These states are leading in the battle against HPV and cervical cancer and will benefit from the preventative care for a lifetime. Fear of the safety of the HPV vaccine is not the only reason parents want vaccination exemptions.

Other issues keeping people from vaccinating include a distrust of government control and the idea that providing a vaccine for what is a sexually transmitted disease sends the message to adolescents that risky sexual behavior is okay. Distrust of government control is not a new concern. People are opposed to federal control over medical treatment and believe that it would be abused and the government would dictate people's medical treatment and exemptions would no longer be discussed on a case-to-case basis[28]. Senator Yen, who is also a physician, is typically a "small government republican", but urges that not requiring vaccinations had led to a public health and safety issue. It is no longer something that can be handled locally, but needs to be addressed at the national level and needs to be enforced before the small outbreaks of measles, mumps, etc. get larger and begin to kill people[7].

The second concern about HPV vaccination is a moral dilemma: do adolescents result in more risky sexual behavior earlier if they are vaccinated against a sexually transmitted disease. Opponents of HPV vaccine requirements claim that HPV vaccination should not be required for public school because it cannot be caught in the classroom via cough, sneeze, touch etc. and

because a student cannot contract the disease except through sexual activity therefore it shouldn't be required to attend school [27]. As mentioned earlier, the HPV vaccination prevents persistent HPV infection, which is present in 98% of cervical cancer cases and leads to at least 250,000 deaths worldwide every year [3]. If a person never initiates sexual activity then theoretically they have no need for the HPV vaccine, but statistics show that over half of sexually-active people will contract HPV at some point and it is impossible to know who will clear the virus by themselves from those that would benefit from the vaccine [30]. Additionally, the national Youth Risk Behavior Survey (YRBS) surveyed 9^{th} - 12^{th} graders from 1991 – 2013 and over 50% report already being sexually-active [31]. When discussing HPV transmission, "sexually active" is defined as participating in oral, anal, or vaginal sex as well as anytime a person's genitals comes into contact with another person. HPV is too serious of a health concern and too easily prevented to put off discussing and accepting adolescent sexual activity.

Demographics of those receiving HPV Vaccination

There are multiple non-moral reasons that prevent people from vaccinating themselves or their kids. Financial barriers to access were mentioned earlier and frequently do keep people in low to middle class from vaccinating. $450/series out of pocket is a very hefty price for a vaccination that is not absolutely mandatory yet. Many low-income families can receive the vaccination through the Vaccines for Children (VFC) program, but slightly higher income families may not have this option available. Other barriers to access include job loss, health insurance loss, single parents, multiple jobs, lack of transportation, and lack of healthcare facility near them [32]. Lack of knowledge and possible language barriers round out the list as potential barriers that prevent parents from being able to vaccinate their children properly [32]. A survey by the National Network for Immunization Information revealed that many parents wanted more

information before they would be willing to vaccinate at all, which shows that a lack of knowledge is a true barrier to vaccine implementation [32].

Previous studies have shown that the demographic of those who participate in HPV vaccinations in the US corresponds with higher socioeconomic status. High socioeconomic families were more likely to participate in vaccinations and at the recommended times. Additionally, high-income families are more likely to participate in age-appropriate cancer screenings, which provides early detection of problems if they do occur. However, statistics also demonstrate that families below the poverty line have slightly higher levels of HPV vaccine coverage compared to their slightly above the poverty line counterparts because of the multiple resources allowing them to get free vaccinations.

From an ethnic/racial standpoint, Hispanics currently have the highest vaccine coverage (47%) followed by African-Americans (39%), Caucasians (38%), then Asian/Pacific Islanders (36%) [33]. American Indians are up to 3 times more likely to have persistent HPV than other Americans even though they are offered free HPV vaccinations under the Vaccines for Children program [34]. This sharp increase is thought to be from a lack of knowledge of HPV vaccination protection. The CDC also released that HPV-associated cervical cancer is higher in African-American and Hispanic women than in white and non-Hispanic women. However, African-American and Hispanic men and women had lower rates of HPV-associated oropharyngeal cancers than their white and non-Hispanic counterparts [35]. These HPV-associated cancers affect more than a million people globally each year and nearly all of these cancers could be avoided by having the complete series of HPV vaccinations.

US HPV Vaccine Coverage

Current HPV vaccine coverage in the United States is approximately 63% in females and 50% in males [36]. Oklahoma, regretfully, only has approximately 39% of females vaccinated and 50% of males vaccinated [36]. These statistics include everyone who has received at least one dose, but not the recommended series of two or three doses. These vaccine rates are far too low to provide adequate population protection from HPV and HPV-associated cancers. To achieve herd immunity protection for non-cancerous vaccine-preventable diseases the threshold needs to be somewhere between 75-95% depending on the method of transmission and level of contagiousness [37]. There has never been a vaccine to prevent cancer so the specific percentage required for herd immunity is unknown, but is thought to need to be comparable to non-cancerous disease percentages. To compare, these are the average vaccine percentages of multiple other vaccines: DTap (84.2%), Polio (93.3%), MMR (91.5%), Hepatitis B (91.6%), and Varicella (91.0%) [36]. These high vaccine compliance rates still show signs that they may be too low to achieve herd immunity, protecting the entire population. Based on that alone researchers are pushing for greater HPV vaccination to hopefully begin eliminating total HPV cases.

The U.S. government has started making HPV vaccination a priority as well. The Office of Disease Prevention and Health Promotion is in charge of making goals to improve the health of the nation. The current set of goals are called Healthy People 2020 and were initiated in 2010 [38]. By 2020 they would like to see complete series HPV vaccination of 80% of females and males. In 2012 the office found the percentages to be 28.1 % and 6.9% for females and males. A 60% increase in vaccine coverage is a very high goal, but it shows that they believe HPV vaccination is an effective means of disease prevention [38]. Other Healthy People 2020

immunization information says that proper immunization reduces direct health care costs by $9.9 billion and saves $33.4 billion in indirect costs. Increases in life expectancy and decreases in the spread of infectious disease are always associated with higher vaccine coverage [38].

Knowing the positive impact increased HPV vaccination would have on the United States; there are a few ways to increase vaccine compliance. HPV vaccine uptake would increase most dramatically if the series of vaccinations were required for entry into public schools. This would cover a wider margin of individuals and if it were mandatory for both girls and boys the results would be very dramatic. If HPV vaccines were required for all 11 – 12 year old students entering public schools (barring a medical exemption) how many of the 6 million cases of HPV would still occur ten or twenty years down the road [39]? Vaccine efficacy research boasts that very few would occur and dramatic reductions in cervical cancer and other HPV-associated cancers would also plummet.

Other ways to increase vaccine compliance falls to physicians or other healthcare providers to speak positively about the HPV vaccine. Many parents are not conscientious of all the vaccines a child needs and when, but health professionals need to be. Similarly, if someone's pediatrician, pharmacist, or nurse tells a parent that the HPV vaccine is not required and treats it as unimportant then that parent will most likely treat it as unimportant as well. The entire health community needs to be well educated on the HPV vaccines potential and when it should be administered. By emphasizing the HPV vaccines importance, safety, and efficacy all health professionals can increase vaccine uptake.

Vaccines for Children (VFC) is doing important work by providing free HPV vaccinations to children who qualify for the program, but those who do not qualify are forced to pay $450 or whatever insurance does not cover for the vaccines. Incentives such as rebates, tax-

refunds, or insurance discounts for those receiving the vaccine will also raise vaccine compliance. The greatest hindrance to vaccine compliance currently is a lack of knowledge of HPV, its consequences, and that the HPV vaccine will prevent it up to 99%. Money spent on HPV vaccine education would be well spent. Information at doctors' offices and schools for parents to read and learn about the vaccines effectiveness and safety would increase vaccine uptake exponentially.

Global HPV Vaccine Coverage

HPV remains a global health concern. However, the United States, Australia, and Western Europe are lowest in HPV infection and death from HPV-associated cancers. This is because each of these developed countries is currently offering HPV vaccinations to the population and encouraging stricter requirements on vaccination [14]. HPV infection and death from HPV-associated cancers is highest in developing countries including sub-Saharan Africa, Melanesia, Latin America, the Caribbean, south-central Asia, and south-east Asia [17]. To put in perspective, 80% of the deaths attributed to HPV worldwide occur in countries such as these. These areas do not have access to pharmaceuticals and do not have screening procedures in place to catch HPV-associated cancers seen in the US. Without screening measures already in place it is actually more cost-effective to initiate preventative vaccinations rather than start screenings such as pap smears. There is also little to no treatment available for those who develop HPV-caused cancers in developing nations. However, there are many groups advocating that vaccinating everyone in the world is a priority and are making a difference in these developing nations. Namesake of the 4vHPV vaccine itself, the Gardasil Access Program has shipped 1.3 million doses of 4vHPV to 21 countries as of July 2016[40].

Table 2 Countries Receiving HPV Vaccines Through the Gardasil Access Program [39]

Honduras	Haiti	Kiribati	Bolivia	Mali	Ghana	Guyana	Cameron
Zambia	Moldova	Georgia	Uganda	Kenya	Tanzania	Lesotho	Mongolia
Nepal	Bhutan	Cambodia	Uzbekistan	Papua New Guinea			

As of 2016, the Gardasil Access Program will fully vaccinate (3 doses) more than 445,900 women who would otherwise be completely unvaccinated [41]. Implementation of these kinds is doubly hard because of transportation of medical supplies and product and reaching people who are currently out of reach of vaccines. After their initial vaccination it is very difficult to make sure the women who received one dose return to receive the subsequent doses of the vaccine. PATH, an innovative company who creates vaccines and medical supplies with developing countries in mind took on multiple HPV vaccination projects in India between 2008 and 2011. In India they supplied and vaccinated 52,755 women thereby preventing the spread of HPV and the development of cervical cancer[41].

The largest entity that is advocating immunizations, including HPV vaccination, in developing countries is GAVI, the Vaccine Alliance[42]. GAVI is based in Geneva, Switzerland and was created in 2000 with the mission to improve access and use of vaccines for children living in the poorest countries in the world. Governments of developed countries across the world such as the UK, US, Sweden, Norway, Canada, and Australia partner with GAVI to increase child immunizations [43]. Currently the United States is in a contract with GAVI to provide $1 billion over 4 years (2015 – 2019) [43]. Private funds are also donated and combined to fund this vaccine-giving giant. Currently, GAVI is supporting 20 or more projects in various countries across Africa and in total approximately 400,000 women are expected to receive life-

saving HPV vaccination [41]. These companies are saving millions of lives annually by providing free and complete HPV vaccinations.

Conclusion

In summary, HPV is a very serious infection affecting millions of men and women in both developed and developing nations every year. The HPV vaccines that are on the market today, 2vHPV, 4vHPV, and 9vHPV, are extremely safe as well as extremely effective at preventing HPV. There is strong evidence supporting HPV vaccines effectiveness and duration even though they are reasonably new. The largest obstacle facing increased HPV vaccinations is a lack of public knowledge and understanding about HPV and HPV vaccines. By educating parents formally on HPV statistics such as half of sexually active people will contract HPV at some point in their life and that 98% of cervical cancer cases are HPV caused, vaccine uptake can be increased [3].

By educating the public that men are just as at risk for several serious types of cancer similar to women more men will seek vaccination for themselves then their sons. Additionally, people will be more open to policy to enact restrictions, which make HPV vaccinations required for children 11 – 12. All of this knowledge will eventually provide well-protected communities for kids to grow and never contract HPV. By never contracting HPV they will never have persistent HPV and as a result will never be a part of the currently 270,000 deaths attributed to HPV caused cervical cancer alone each year [3]. As HPV vaccine compliance continues to rise and the evidence continues to show how it is making a positive difference in countries will continue to support groups such as GAVI who are reaching formally unreached people with life-saving vaccines. HPV is a 99% preventable disease that has not been beaten. Now is the time to get vaccinated and educate all people on the importance of the HPV vaccine. [44]

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